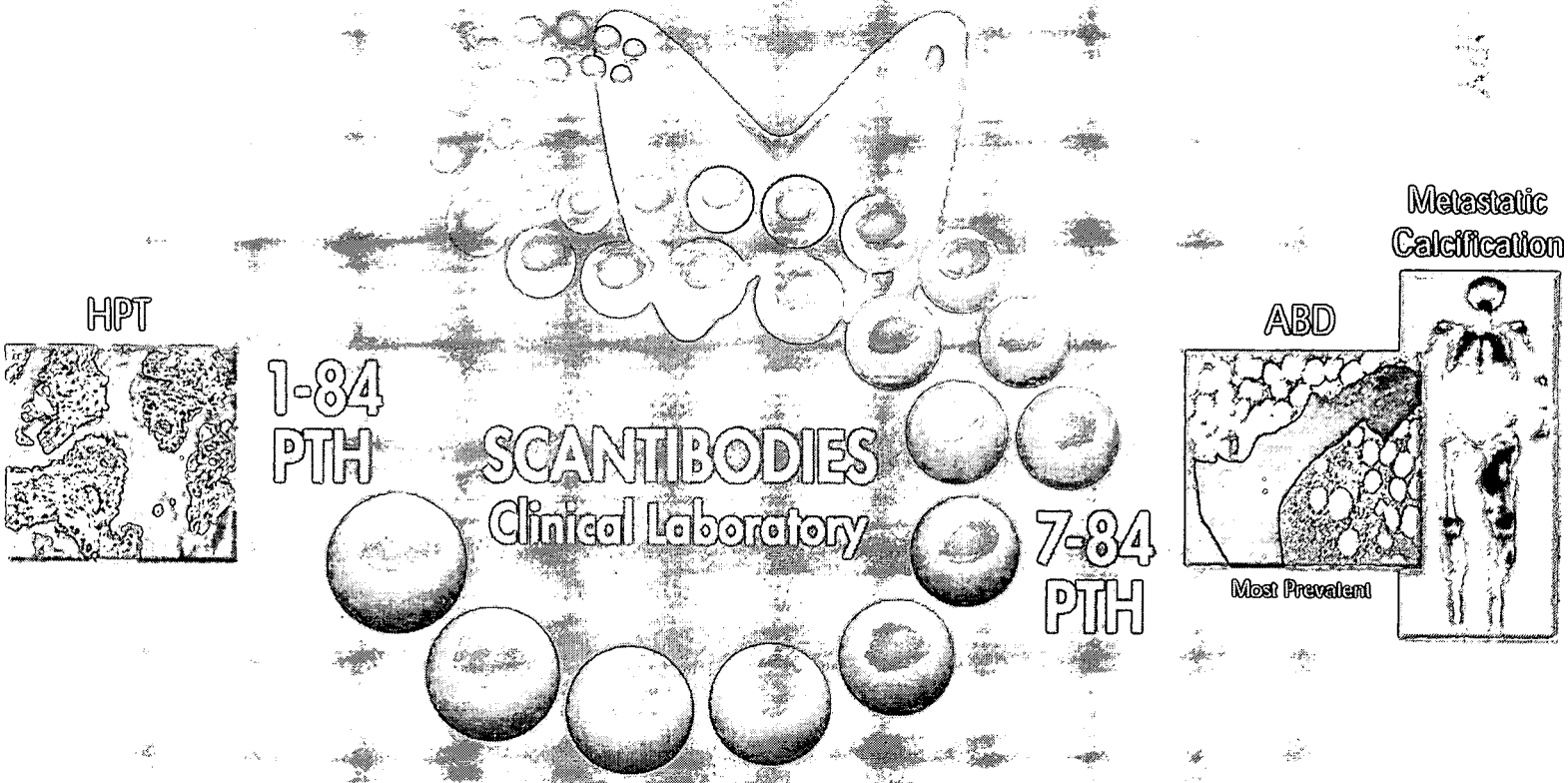
The Clinical Benefits of the Specific 1-84 PTH Assay that Measures PTH within the Physiological Range

Improvement in Renal Bone and Calcium Metabolism Management

by Tom Cantor, President, SCI and Life-Long PTH Researcher

Re: Application No: 10/617,489
Filed: July 10, 2003
Atty. Docket No. 53221/2000623



50,000 New Cases of Primary Hyperparathyroidism are Diagnosed Every Year in the US

Parathyroidectomy Treatment is Safe & Effective

Left Untreated Primary Hyperparathyroidism is Life Threatening Affecting Bones, Nerves, Muscles and Mental Function and Usually is Accompanied with Hypercalcemia

(Hypercalcemia May Be Due to Cancer)

The PTH Assay is Heavily Relied Upon for Differential Dagnosis

The Commonly Used intact PTH Assay
that is not able to distinguish between 1-84 PTH & 7-84 PTH
is Only 72% Accurate for
Predicting Primary Hyperparathyroidism

But,

The Specific 1-84 PTH Assay

is
96% Accurate for Predicting Primary Hyperparathyroidism

0021-972X/03/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 88(10):4725–4730

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Clinical Utility of an Immunoradiometric Assay for Parathyroid Hormone (1–84) in Primary Hyperparathyroidism

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The reliable diagnosis of primary hyperparathyroidism depends on the measurement of PTH. The PTH assays in widespread use measure not only the hormone but also hormone fragments, thus limiting the clinical utility of the assays. A new immunoradiometric assay (IRMA) using an antigenic determinant at the extreme amino-terminal of the PTH molecule detects only full-length PTH (1–84). We compared three PTH assays and determined the presence of PTH (1–84) and PTH fragments in serum and parathyroid adenomas of patients with primary hyperparathyroidism. We studied 56 patients with primary hyperparathyroidism. PTH levels were increased in 63% using the midmolecule RIA; in 73% in the "intact" IRMA; and in 96% in the PTH (1–84)-IRMA. The PTH (1–84)-IRMA correlated with the other assays (midmolecule RIA R = +0.736; $P < 0.0001$; "intact"-IRMA R = +0.951; $P < 0.0001$) and indices of disease activity (serum calcium R = +0.511, $P < 0.0001$; alkaline phosphatase R = +0.489, $P = 0.001$; and radius bone density R = −0.366, $P < 0.01$). In 21 consecutive patients undergoing parathyroidectomy, 18 had parathyroid adenomas. Intact PTH was higher than PTH (1–84)-IRMA in both serum and glandular homogenates from these patients. Similar proportions of PTH (1–84) and hormone fragments were found in both adenomas [66 ± 3% of "intact" PTH-reflected PTH (1–84) and sera (73 ± 2% of "intact" PTH reflected PTH (1–84)]. We conclude that the PTH (1–84)-IRMA offers improved diagnostic sensitivity in patients with primary hyperparathyroidism than other currently available assays. This study also provides evidence that both PTH (1–84) and PTH fragments are produced in parathyroid adenomas and that peripheral metabolism of hormone and fragment does not alter the proportion of bioactive hormone. (*J Clin Endocrinol Metab* 88: 4725–4730, 2003)

THE DEVELOPMENT OF improved assays for the measurement of PTH in the circulation has had a significant impact on the diagnosis and understanding of parathyroid gland dysfunction (1–5). However, efforts in this regard have been hampered by the presence of PTH fragments (5–8). PTH assays commonly measured these fragments, thus confounding attempts to determine true levels of bioactive hormone.

Inactive carboxy-terminal fragments of PTH are generated by metabolism of hormone in the circulation, within the liver, in the parathyroid gland itself, and conceivably in other organs (5, 6, 9–12). These fragments are eliminated primarily by the kidney. Early measurements of PTH by RIA often used antisera directed against midregion or carboxy-terminal epitopes of undefined biological activity. These assays measured active PTH as well as the carboxy-terminal fragments, posing a particular problem in patients with impaired renal function, in whom fragments typically accumulate.

The introduction of the immunoradiometric assay (IRMA) offered important advantages over the RIA. Assays based on antibodies directed against epitopes on both the carboxy- and the amino-terminal aspects of the PTH molecule were designed to exclude carboxy-terminal fragments from the measurements of biologically active hormone. To a certain extent, the first-generation IRMA method achieved this goal. However, in 1998, LePage *et al.* (7) demonstrated a large non-(1–84) PTH fragment that was not excluded by the "intact" IRMA for PTH. This large fragment comigrated with PTH (7–84) and had substantial cross-reactivity in commercially available IRMAs. It constituted as much as 50% (20–90%) of immunoreactivity by IRMA for PTH in individuals with chronic renal failure (13).

A new IRMA uses affinity-purified polyclonal antibodies to the (39–84) and (1–4) amino acid regions of PTH (8, 13). Recognition of PTH in this assay requires that the entire PTH molecule must be intact, including the extreme end of the amino-terminal aspects of the PTH molecule. This assay, therefore, does not detect the large the fragment that circulates in normal patients. An assay specific for PTH (1–84) may have clinical utility in uremic patients. Renal failure patients clearly have secondary hyperparathyroidism, yet the "intact"-IRMA has been shown to considerably overestimate elevations in biologically active hormone concentration (7, 14, 15). In primary hyperparathyroidism, a large non-(1–84) PTH fragment is detected as well (13). In this study, the utility of this new IRMA for PTH (1–84) was assessed in a group of patients with primary hyperparathyroidism. Using the data obtained from simultaneous measurement of PTH in several assays, we investigated the presence of PTH (1–84) and PTH fragment in the adenomatous glands and in the circulation of patients with primary hyperparathyroidism.

Abbreviation: IRMA, Immunoradiometric assay.

Fig. 34

Primary Data of Dr. S. Silverberg's Study

Diagnostic Sensitivity	55% (nr =70-220)	73.2% (nr = 10-65)	96.4% (nr = 7-36)	Ca^{++}
ID	1st Generation DiaSorin MM-PTH Assay	2nd Generation Nichols Intact PTH Assay	3rd Generation SLI/CAP™ Assay	
215	344	35.37	39.54	10.9
216	351	131.41	79.78	11.6
217	818	204.34	150.01	11.3
218	89	58.16	46.62	11.8
219	103	88.58	53.38	11.0
220	168	98.30	63.46	10.8
221	2409	331.17	319.40	13.0
224	67	55.29	44.16	10.6
356	416	82.45	49.85	11.0
357	44	74.83	49.40	9.9
358	85	49.49	36.71	10.3
360	76	48.45	36.82	10.7
362	668	136.68	74.40	10.8
363	74	35.12	26.62	11.2
364	107	60.12	56.38	10.6
365	183	114.03	75.289	11.8
435	81	67.64	54.99	
436	388	116.82	88.66	10.6
438	252	77.82	47.08	10.9
439	246	110.41	67.61	10.5
440	211	81.84	48.12	11.0
441	1152	148.31	98.80	12.7
442	565	90.84	53.43	10.9
443	485	138.27	95.82	12.4
445	150	70.93	50.87	11.6
635	377	92.19	51.43	10.5
637	1189	153.89	99.35	10.5
638	223	48.72	51.45	11.0
639	67	53.85	46.33	11.1
642	428	103.57	76.49	11.4
673	854	147.20	125.89	10.5
675	378	79.38	68.93	10.4
676	454	115.60	79.74	11.1
756	366	86.16	64.60	10.6
757	766	113.07	106.69	10.6
758	197	95.15	70.40	10.8
759	318	36.58	30.94	9.9
761	186	78.08	70.36	10.2
762	2724	131.74	91.86	10.9
763	1626	180.47	127.67	10.0
764	1423	250.30	175.30	12.4
765	55	40.83	29.26	10.4
872	306	113.30	71.76	10.0
873	42	64.86	52.02	10.2
874	318	103.54	75.45	10.6
875	89	63.41	35.71	10.4
876	200	57.54	40.23	11.1
877	767	227.99	183.05	11.2
878	95	54.81	43.86	10.5
880	185	83.74	60.16	10.8
881	770	92.53	59.49	10.3
894	845	142.57	91.85	11.3
896	267	97.30	75.69	10.2
897	1021	168.06	97.64	10.8
899	1	80.80	60.29	10.3
900	205	86.70	84.15	10.8

= Diagnostic dilemmas

One of the Most Serious Complications to Kidney Failure is Secondary Hyperparathyroidism

Which Leads to

Bone Disease

Which Leads to

Disturbances in Mineral Metabolism

Which Leads to

Vascular & Soft Tissue Calcification

Which Leads to the Leading Cause of Death for Dialysis Patient

Myocardial Infarction

Example:

If a 20 Year Old Starts Dialysis Today & Asks,

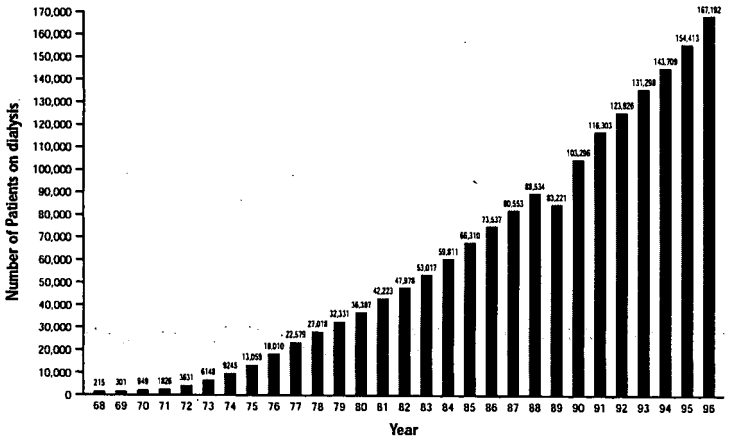
"What Are My Chances of a Cardiac Event Within the Next Year?"

The Answer is:

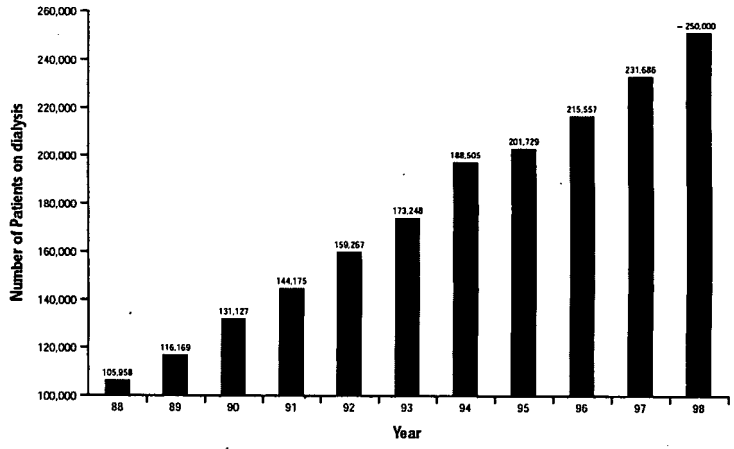
"The Same as an 85 Year Old!"

Number of Patients on Renal Dialysis in Japan

In 1996 – 28,234 new cases per year
Projection for year 2000 – 225,000

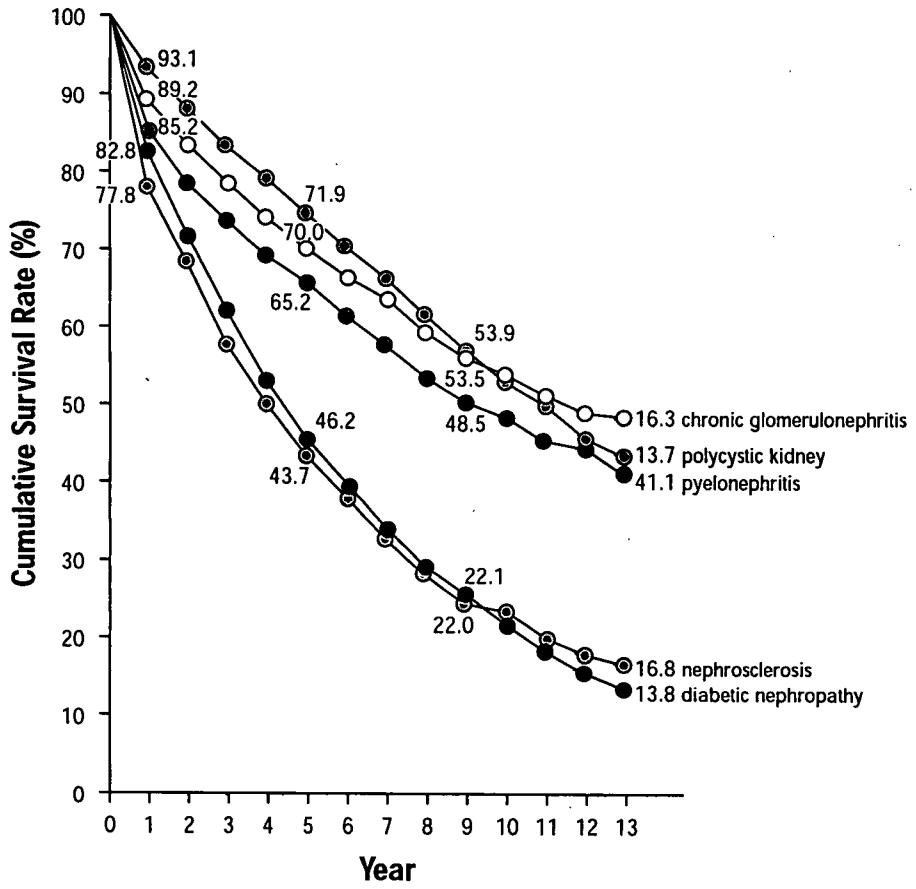


Number of Patients on Renal Dialysis in the USA



SCANTIBODIES CLINICAL LABORATORY

Survival Rates for CRF Patients in Japan



SCL SCANTIBODIES CLINICAL LABORATORY

The Dilemma:

Why Should the Country with the Most Expenditures for ESRD Patients have the Highest Mortality Rate?

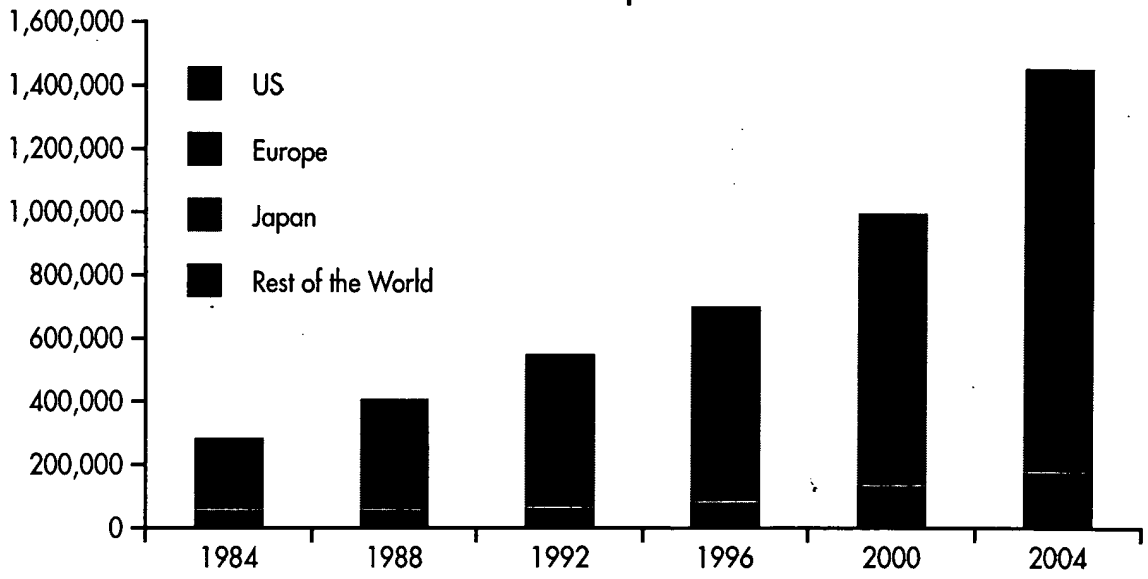
Why does the U.S. spend today nearly twice as much than the UK on health 30 years ago?

The US government spends over $22 billion per year on health care for Dialysis Patients.

In spite of this expenditure, the following problems occur:

The number of End Stage Renal Disease (ESRD) patients continues to grow at a higher rate than may be attributed to population growth.

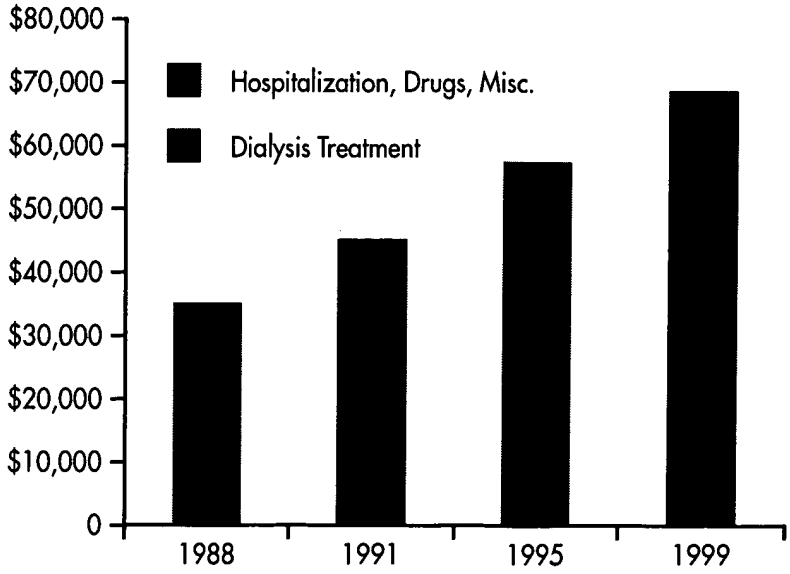
ESRD Patient Population



Worldwide Patient Population

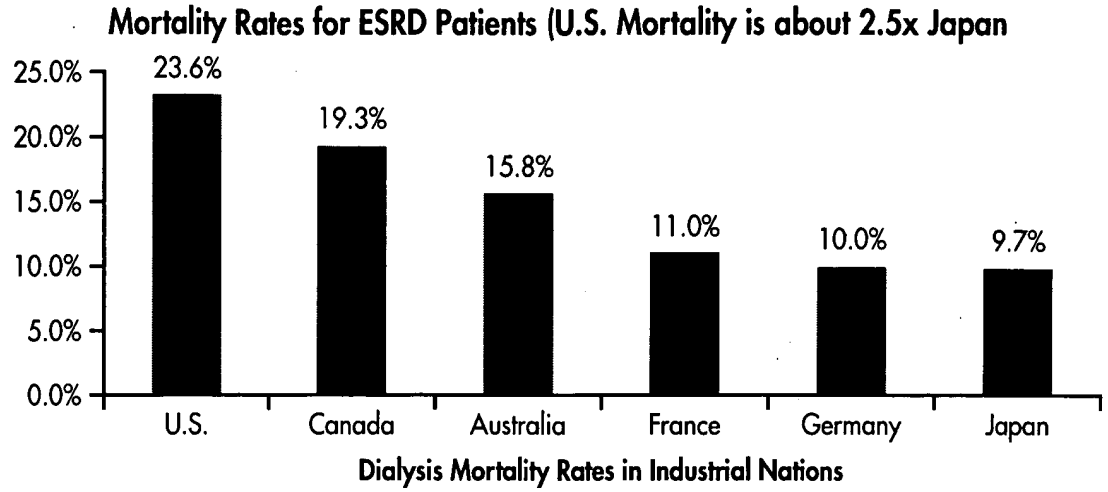
The US government spends the most amount of money per patient when compared to that of other countries. $65,000 per year/per patient represents over $22 billion per year of government expenditure.

The U.S. Costs per ESRD Patient for Dialysis Services vs Drugs, Hospitalization, etc.



Dialysis Treatment based on composite rate

However, the tragedy is that the mortality rate for ESRD patients in the US is the worst in the world (2.5 times higher than in Japan).



Why should the country which spends the most $ per patient for ESRD treatments and the highest amount of spending for research have the highest (worst) mortality when compared to the world's other countries? With dramatic increases in the cost of treatment why does the ESRD Patient today not live one day longer than the ESRD Patient did 30 years ago?

There is an Epidemic of the Mortal Condition of Soft Tissue & Vascular Calcification Among End Stage Renal Disease (ESRD) Patients

There has been an Increase in Calcification

Kidney International
Volume 61 Issue 6 Page 2210 - June 2002

Calciphylaxis is usually non-ulcerating: Risk factors, outcome and therapy

Adrian Fine and James Zacharias

Calciphylaxis is usually non-ulcerating: Risk factors, outcome and therapy.

Background. Calciphylaxis, historically considered rare, seems to be increasing in frequency. In our single center, 36 new cases have accumulated in seven years. The majority of these cases were non-ulcerating, which we believe to be early disease, in contradistinction to the vast majority of published cases that presented with ulcers.

Methods. Prospective data were collected on all patients with calciphylaxis. As well, a case control study, with two controls per patient, was performed on patients presenting with non-ulcerating plaques.

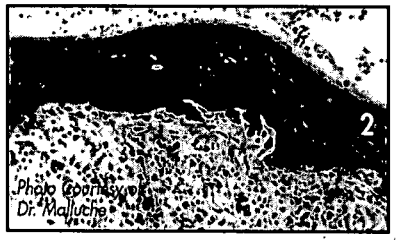
Results. The incidence of calciphylaxis in dialysis patients increased with a rate of 4.5/100 patient-years in the past three years. Eighty percent of cases presented with non-ulcerating subcutaneous plaques in the calves, easily confused with cellulitis. In those patients presenting with plaques only, the mortality rate was 33% at six months. Once ulceration develops, the mortality rate increased to above 80%. Bone scan was positive in 97% of patients. Steroid therapy appeared to be beneficial in some patients. Peritoneal dialysis, female sex and diabetes were risk factors. In the case control study of patients presenting with plaques only, serum phosphate (OR 2.6; 95% CI 1.05 to 6.45, $P = 0.038$) and Ca P product (OR 1.46; 95% CI 1.02 to 20, $P = 0.038$) predicted the disease, as did being on calcium salts + vitamin D (OR 4.05; 95% CI 1.14 to 14.5, $P = 0.03$).

Conclusions. Calciphylaxis is no longer rare. It is usually nonulcerating and can be diagnosed clinically in all patients. These patients have a high mortality, especially once ulceration occurs. Calcium salts plus vitamin D, as well as serum Ca P product and high serum P increase the chance of the diseases. Therefore, the disease may be preventable. Steroids may be of benefit to some patients.

Innaccurate (over estimating) PTH Assays May Lead to Misguided (Over) Suppression with Vitamin D Resulting in Calcification Affecting Bones, Digits and Joints

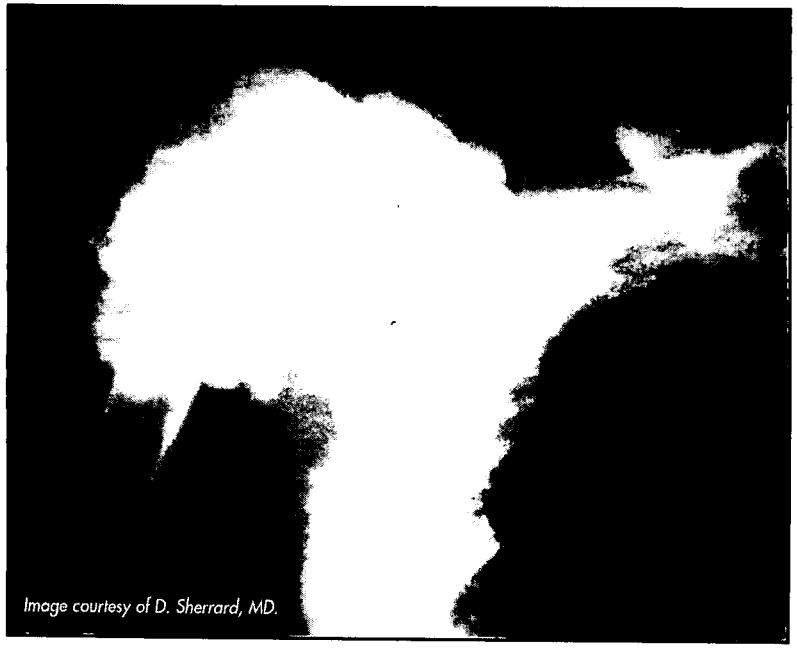
The Bones

Clinical Manifestations of 2° Hyperparathyroidism

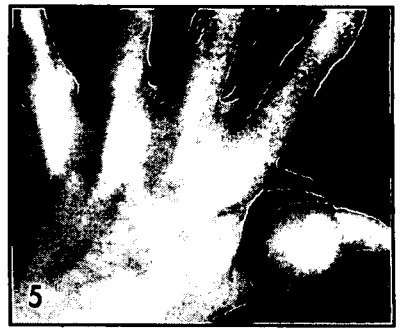


The Joints

Articular metastatic calcification; shoulder.



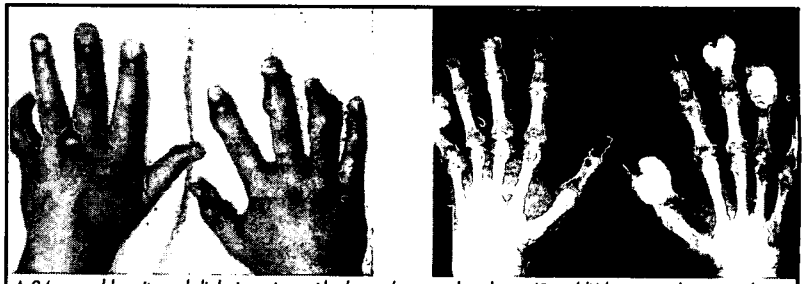
The Digits



Left: Developmental factors of secondary hyperparathyroidism.
1) Bone segment of renal dialysis patient showing secondary hyperparathyroid bone disease.
2) Improved bone condition after oral therapy with 1,25 $(OH)_2$ D_3.
3) Disintegration of toes following kidney transplant. **4)** Healing of lesions after subtotal parathyroidectomy.
5) Nodules on fingers of renal dialysis patient.

Chart Courtesy of Eduardo Slatopolsky and James A. Delmez. Metabolic Bone Disease cc1998

Periarticular metastatic calcification; hand.



A 24-year-old peritoneal dialysis patient with elevated serum phosphorus (9mg/dL) but normal serum calcium presented with pain and swelling in the joints of her hands (left). Radiographs (right) revealed periarticular calcifications. With control of her phosphorus level, the calcifications decreased but failed to completely resolve. Periarticular calcifications are often visible radiologically but are usually asymptomatic. However, they may progress to large deposits,[43] precipitate arthritic attacks, or limit the range of affected joints.[48]

Photographs from Sharon M. Moe, MD.

Innaccurate (over estimating) PTH Assays May Lead to Misguided (Over) Suppression with Vitamin D Resulting in Calcification Affecting the Skin

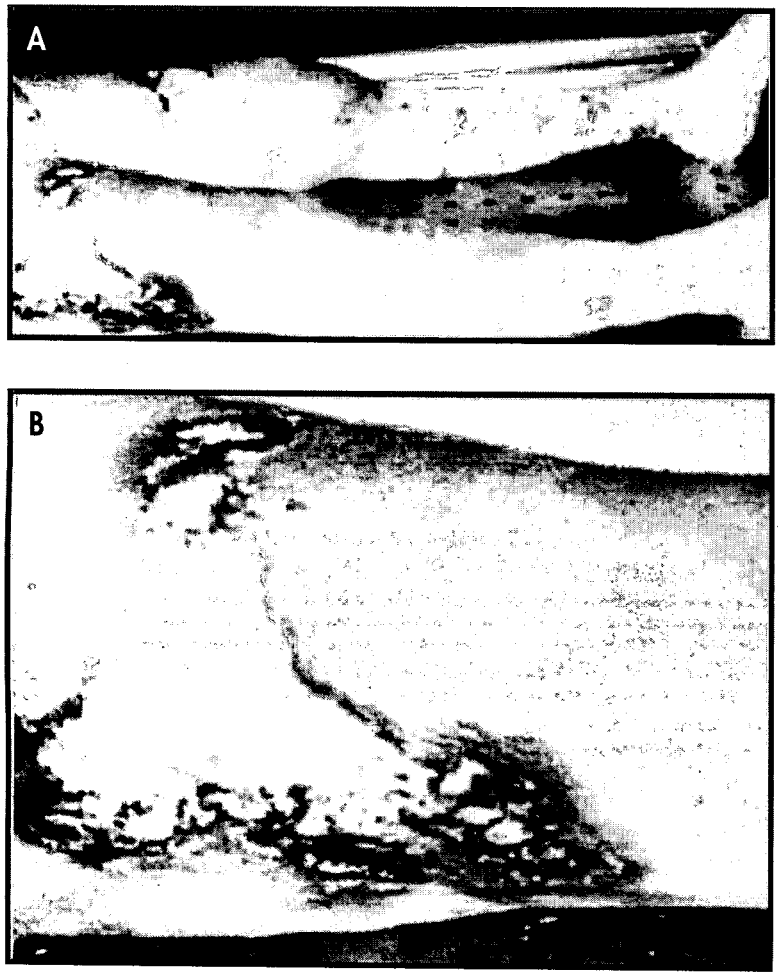


Figure 1. Ulcers on the Lower Legs and Thighs (Panel A) and on the Right Thigh (Panel B).

NEJM – Baran and Letts 345 (15): 1119 Figure 4

Case 31-2001 – Photos show a seventy year old woman with end -stage renal disease and cutaneous ulcers.

Figure 2. Ulcer around the Nipple of the Right Breast.

NEJM – Baran and Letts 345 (15): 1119 Figure 2

Innaccurate (over estimating) PTH Assays May Lead to Misguided (Over) Suppression with Vitamin D Resulting in Calcification Affecting the Soft Tissue Organs, Nerves and Blood Vessels

The Organs (Lungs)

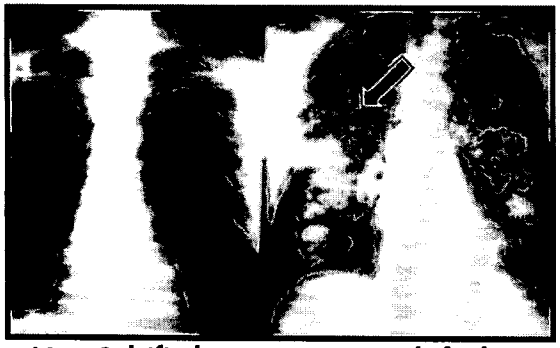


Figure 15. Mastatatic Calcification of the lungs.

Images courtesy of Eduardo Slatopolsky, MD

The Nerves

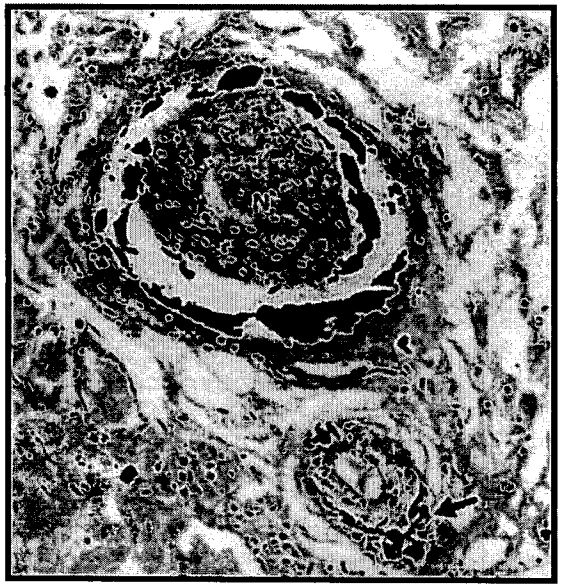


Figure 6. A subcutaneous Nerve (N) surrounded by Calcific Material and a subcutaneous artery with Calcific Material in the wall (arrow) (von Kossa's Stain, x200)

NEJM – Baran and Letts 345 (15): 1119 Figure 6

The Blood Vessels

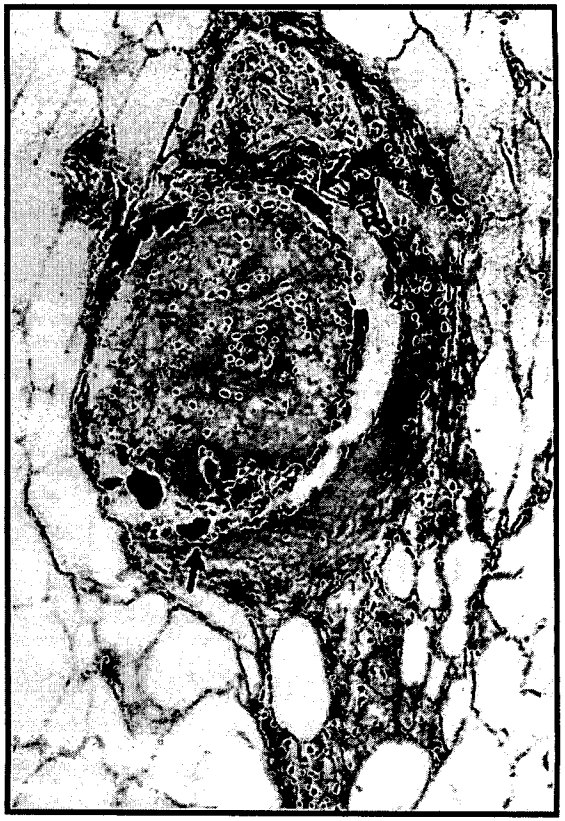


Figure 4. A subcutaneous artery with Calcific Material in the media (arrows) and Occlusive Hyperplasia of the Intima (Hematoxylin and Eosin, x250).

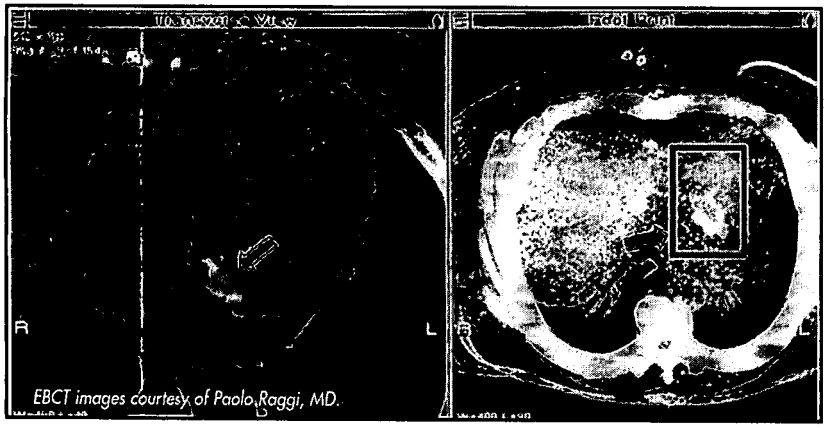
NEJM – Baran and Letts 345 (15): 1119 Figure 4

Innaccurate (over estimating) PTH Assays May Lead to Misguided (Over) Suppression with Vitamin D Resulting in Calcification Affecting the Heart

The Heart

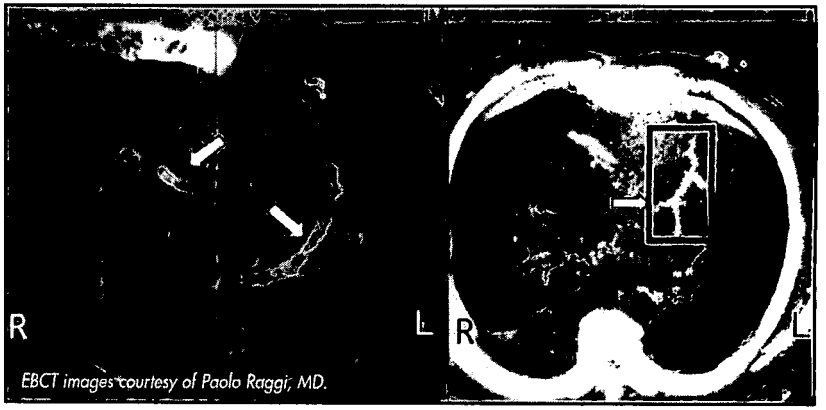
Heart Valves

EBCT scan of mitral valve calcification in a dialysis patient.

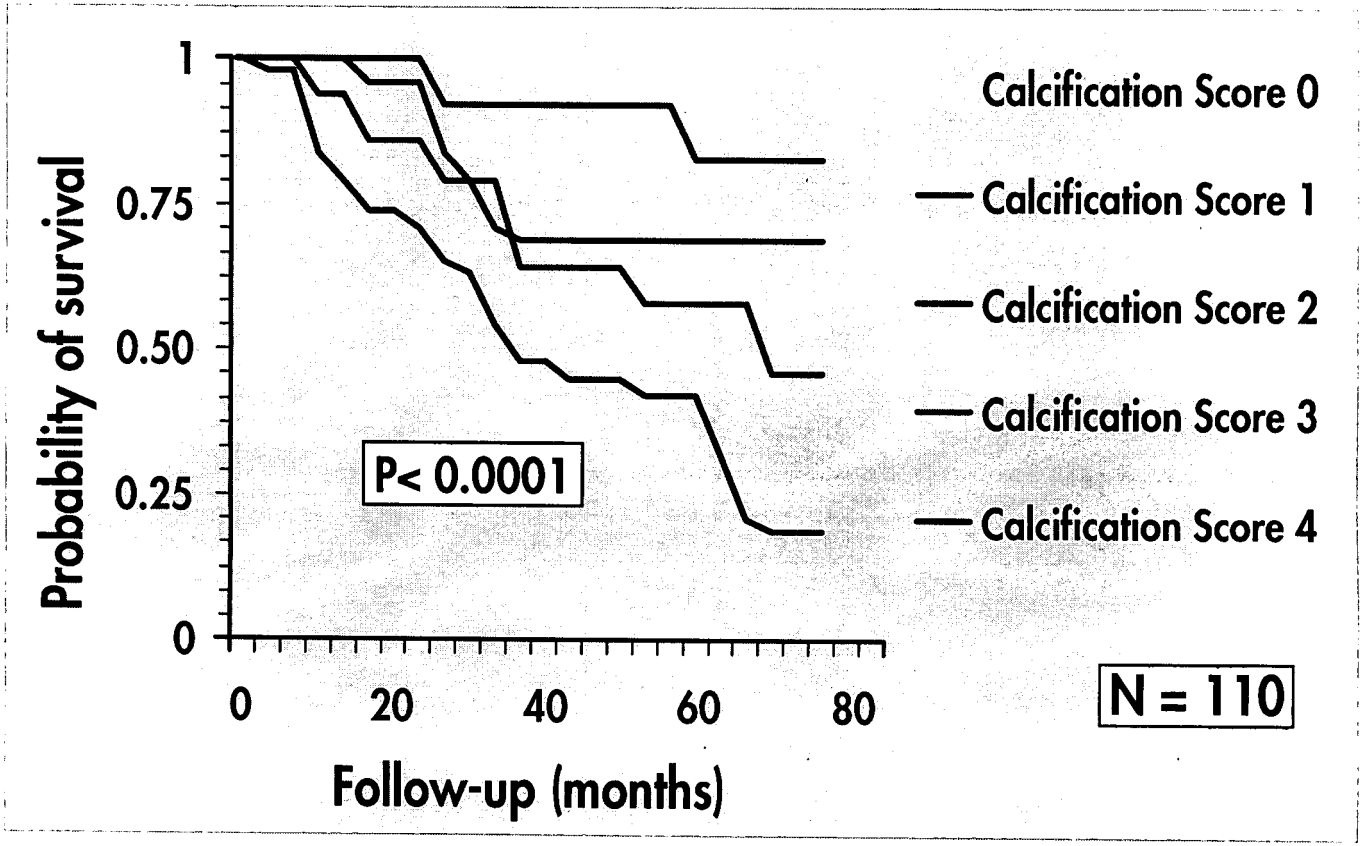


Coronary Arteries

Electron beam computed tomography (EBCT) scans showing extensive calcification of coronary arteries in a dialysis patient, indicating advanced disease.



Calcification Score and Mortality

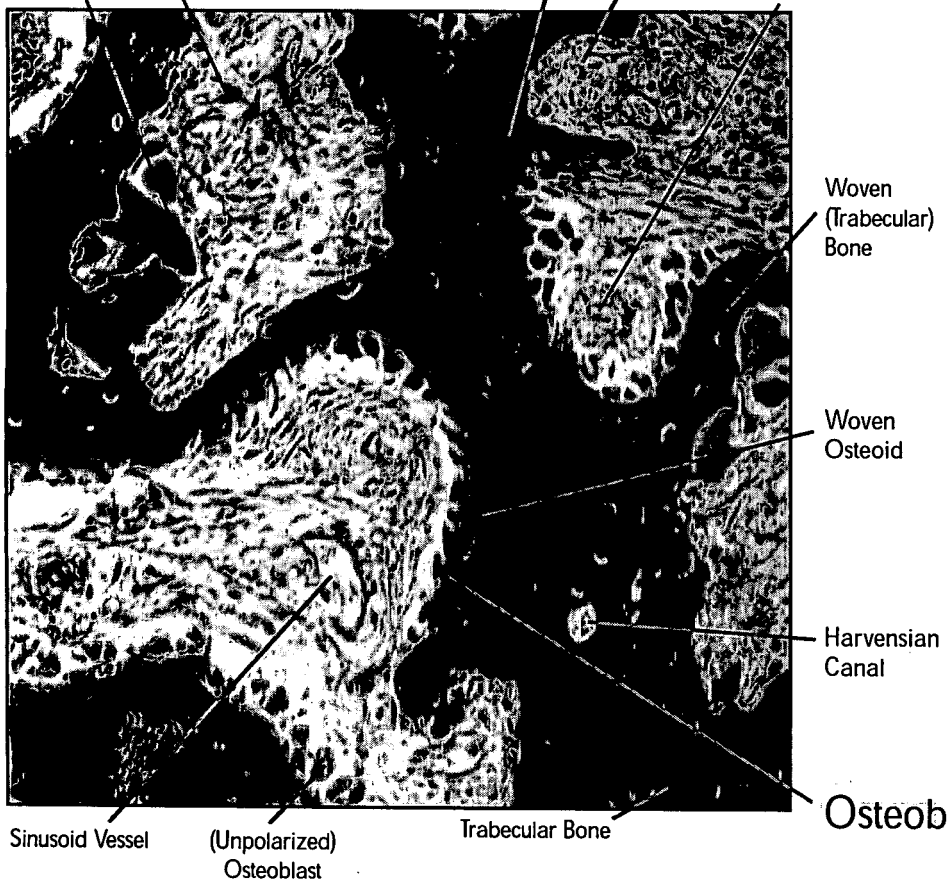


Blacher J, *Hypertension 2001; 38:938-942*

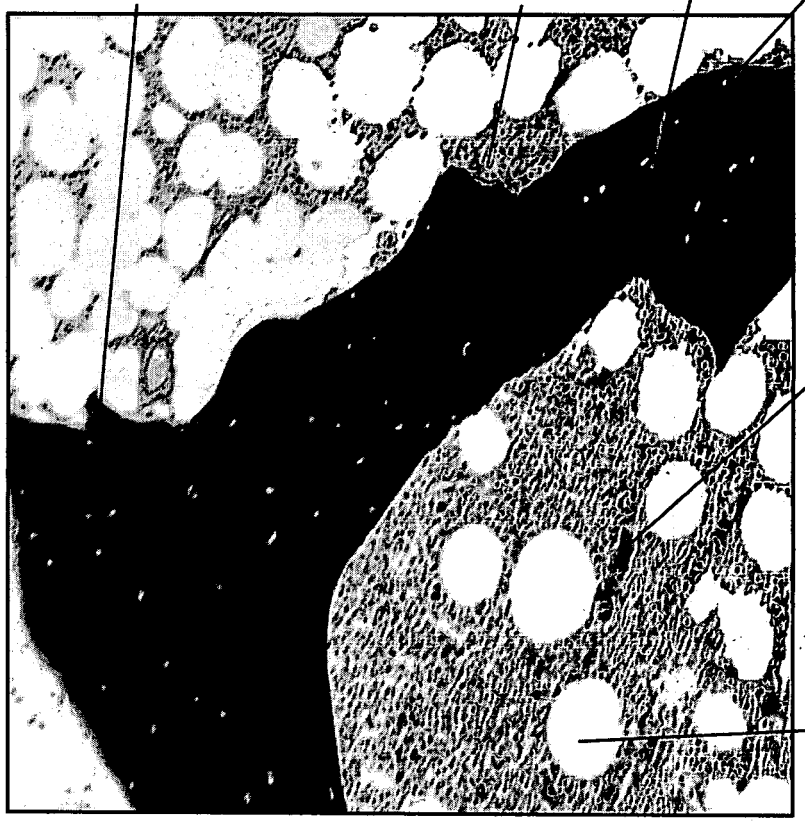
There is An Epidemic of Adynamic Bone Disease Among ESRD Patients

The Histological Difference Between High Bone Turnover Disease (Hyperparathyroidism) and Adynamic Bone Disease

HPT



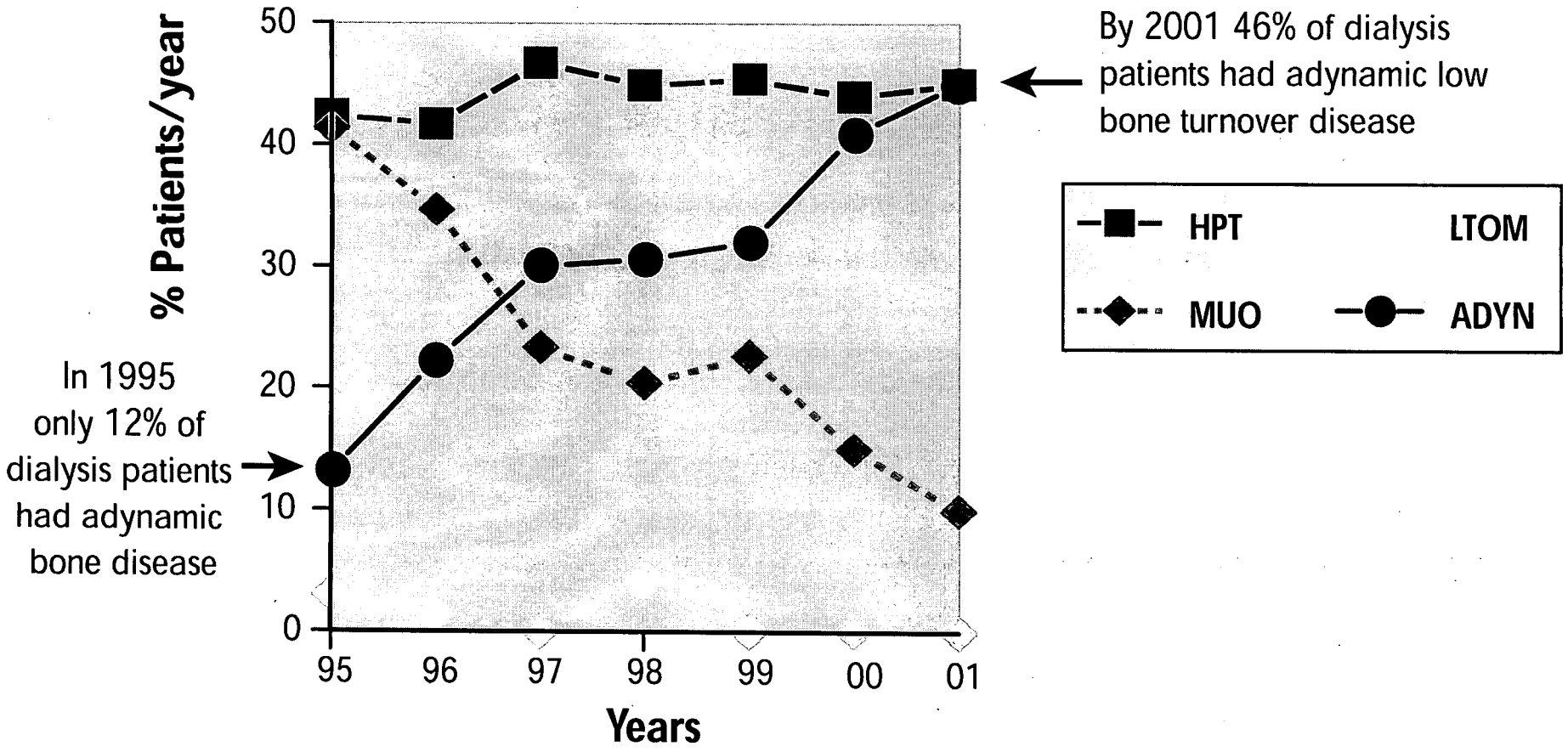
ABD



Note how in ABD bone there is an absence of osteoclasts, osteoblasts, and osteoids which indicates a total absence of bone turnover.

Division of Nephrology, Bone and Mineral Metabolism, University of Kentucky Medical Center, Lexington, USA.

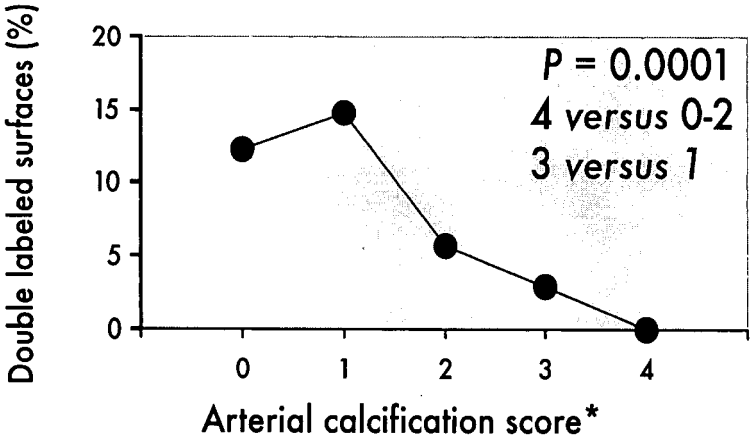
The Rise in Adynamic Bone Disease in ESRD Patients and the Changing Spectrum of Renal Osteodystrophy

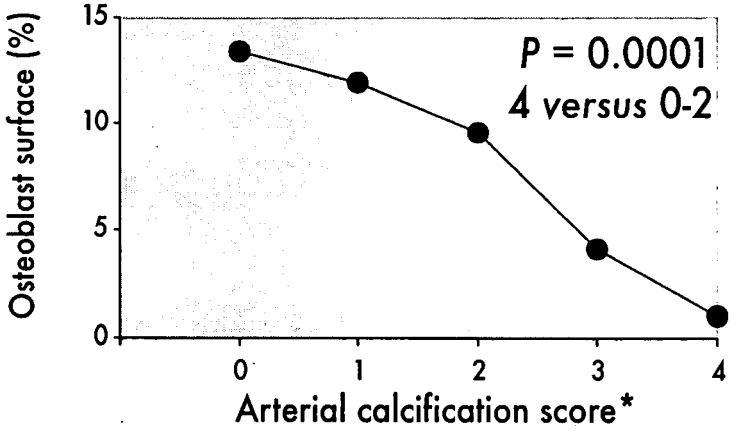


>2000 pts bone biopsy data from Dr. Malluche presented at the WCN/ERA/EDTA Berlin 2003 Conference and Malluche et al, *Clin Nephrol 1999*

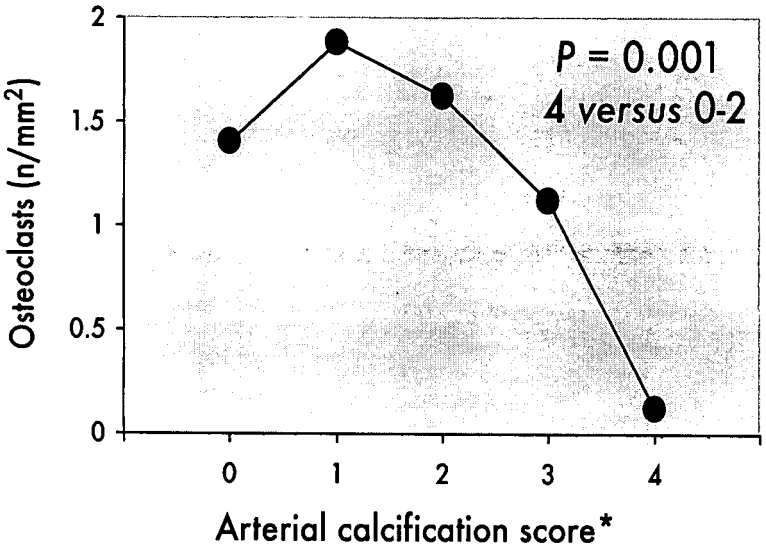
Arterial Calcification is Associated Exclusively with Adynamic Bone Disease

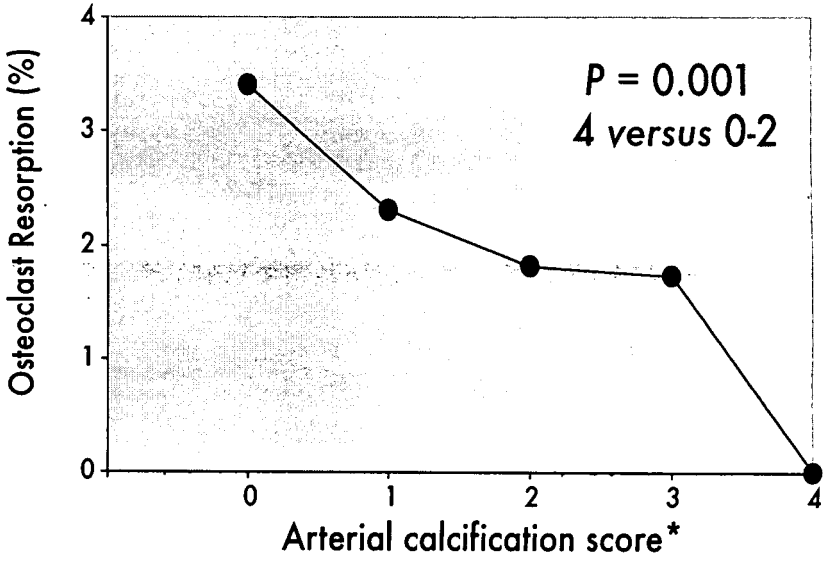
Arterial Calcifications and Bone Histomorphometry in ESRD





n = 58

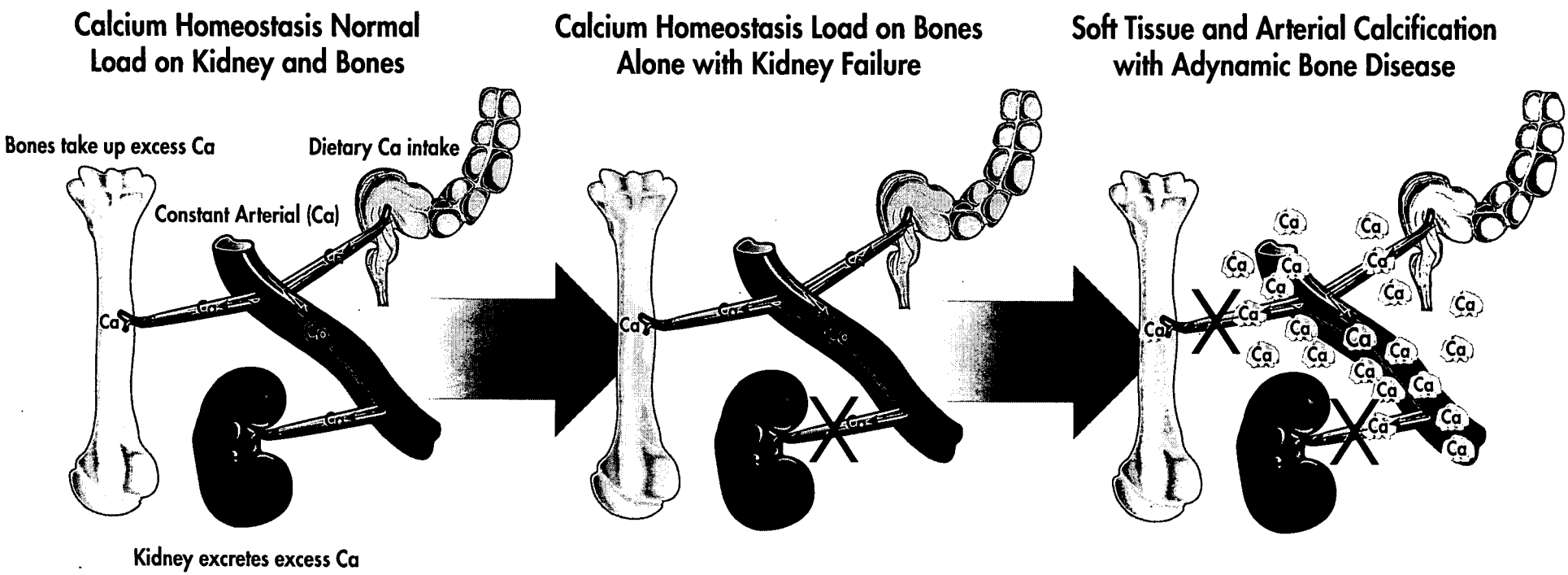


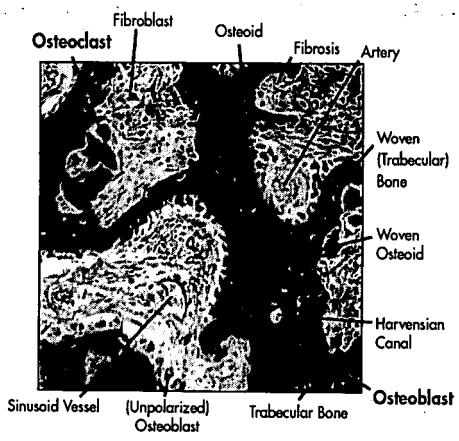


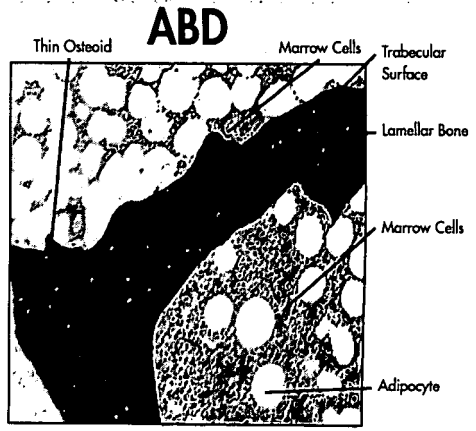
***Determined by ultrasonography**

London GM, Marty C, Marchais SJ, Guerin AP, Metivier F, De Vernejoul M-C. Arterial Calcifications and Bone Histomorphometry in End-Stage Renal Disease. *J Am Soc Nephrol 2004; 15:1943-1951.*

How Adynamic Bone Disease with Kidney Failure Results in Soft Tissue and Arterial Calcification





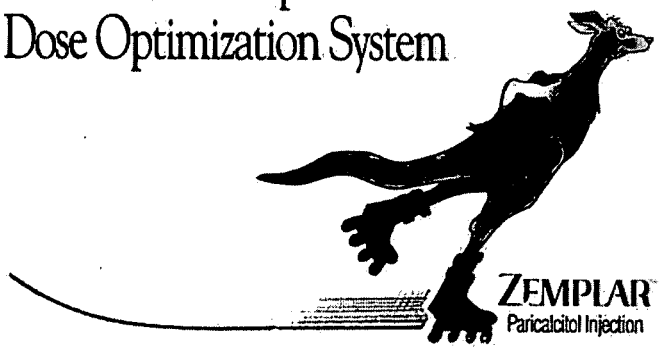


Potent Vitamin D Analogs are used to Treat Between 60% -80% of ESRD Patients & The Commonly Used Intact PTH Assay (that Does Not Distinguish 1-84 PTH from 7-84 PTH)

is Heavily Relied Upon for Vitamin D Treatment Decisions (Low PTH Values Indicate Adynamic Bone Disease & Disqualify the Patient From Vitamin D Therapy)

For Fast, Smooth Control

Choose the Zemplar Dose Optimization System



The Zemplar Dose Optimization System

Safe, Simple, Effective Dosing

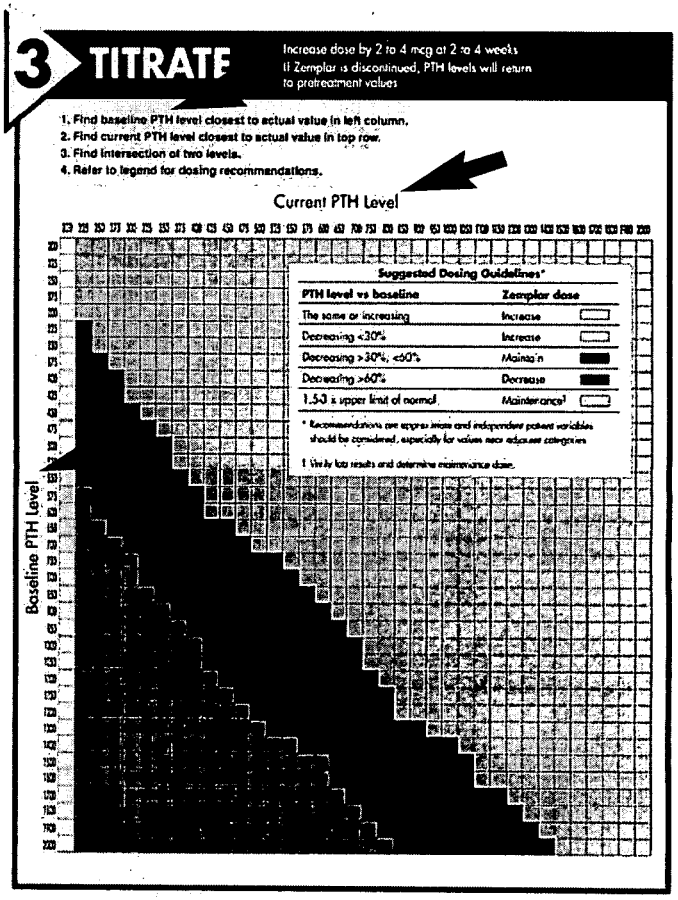
Step 1: Initiate > **Step 2: Evaluate** > **Step 3: Titrate**

Important Safety Considerations

Zemplar is contraindicated in patients with vitamin D toxicity, hypercalcemia, or hypersensitivity to product ingredients. Phosphate or vitamin D–related compounds should be discontinued.

Administration may place patients at risk for hypercalcemia, elevated Ca × P product, and metastatic calcification.

Vitamin D Treatment is guided solely by the PTH Assay

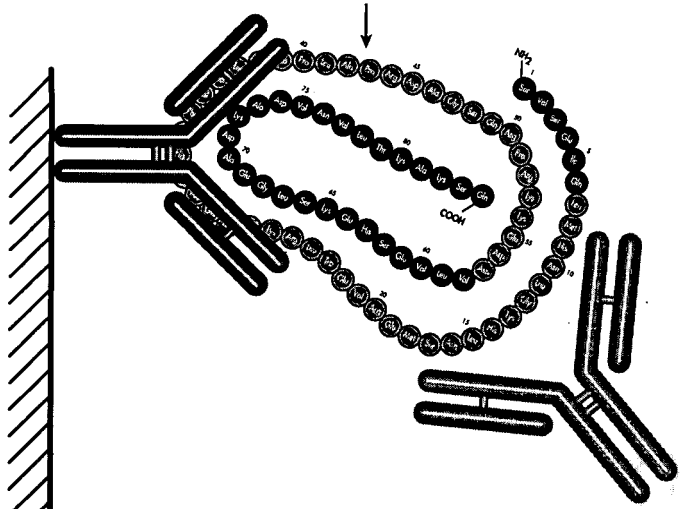


Essential Laboratory Tests: Measurements of serum or plasma PTH and recommended every 3 months. An intact PTH (iPTH) assay is recommended for reliable detection of biologically active PTH in patients with CRF. During dose adjustment of Zemplar™, laboratory tests may be required more frequently.

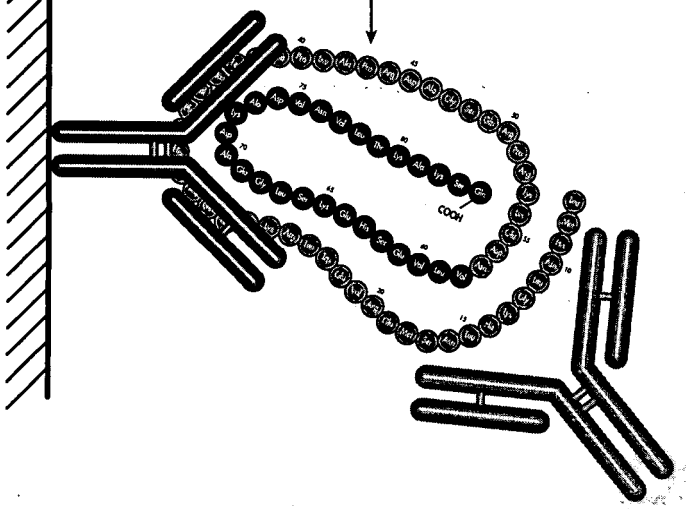
2nd Generation "Intact" PTH Assay

that Does N Distinguish Between 1-84 PTH and 7-84 PTH

CAP™ or 1-84 PTH



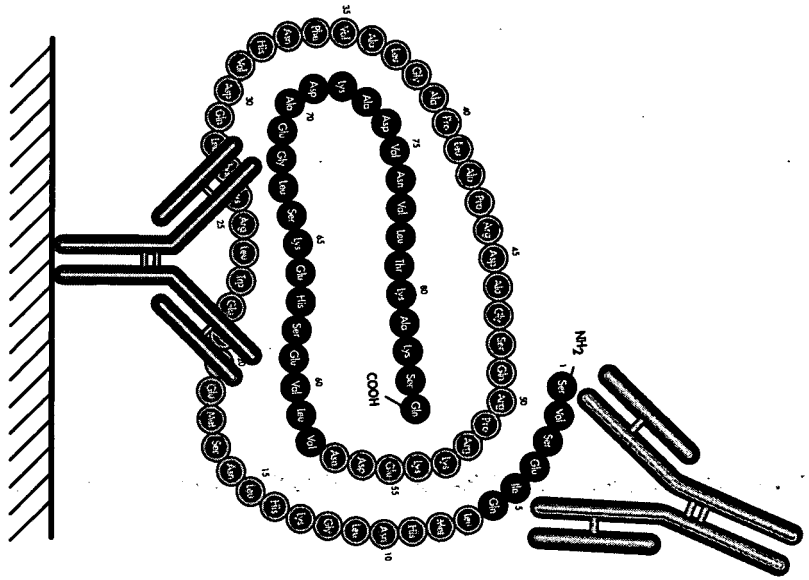
CIP™ or 7-84 PTH Fragment



3rd Generation PTH Assay Measures PTH within the Physiological Range

3rd Generation CAP™ (1-84 PTH) Assay

That will not Measure 7-84 PTH



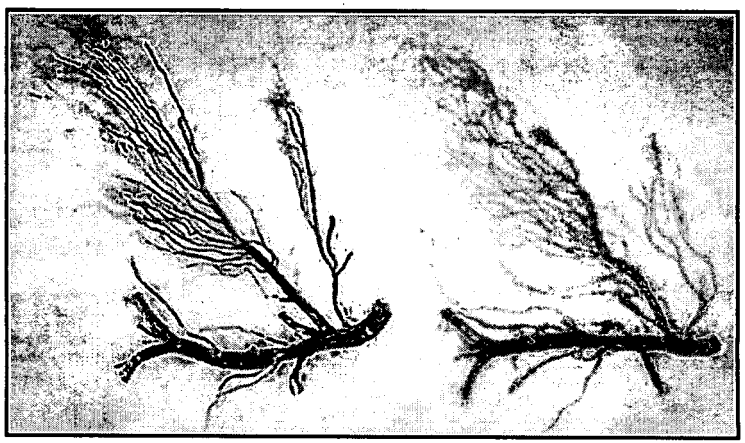
Label antibody reacting with farthest most amino acids

Gao P, Scheibel S, D'Amour P, et al. Development of a Novel Immunoradiometric Assay Exclusively for Biologically Active Whole Parathyroid Hormone 1-84: Implications for Improvement of Accurate Assessment of Parathyroid Function. *J Bone Miner Res 2001; 16(4):605-614.*

The Mortal Side Effect of Vitamin D is Vascular Calcification

Vitamin D Calcifies Arteries in the Rat Within Hours

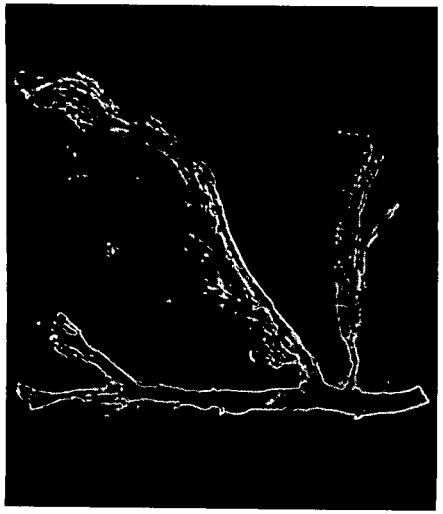
Vitamin D-Treated



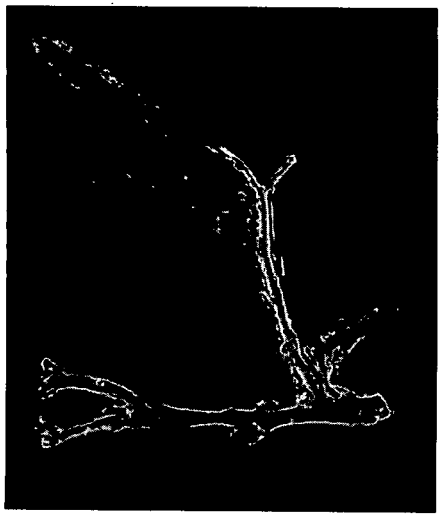
Age-Matched Control

Time of Vitamin D Treatment

48 Hours

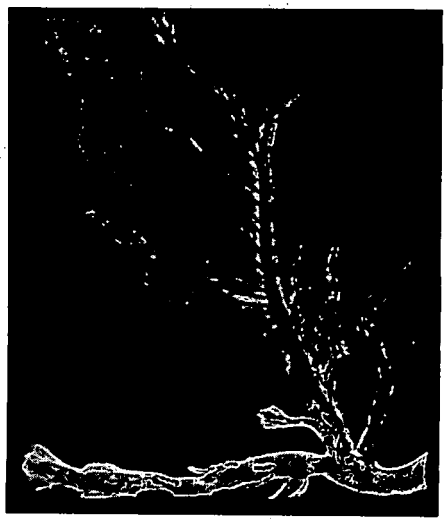


72 Hours



84 Hours

96 Hours

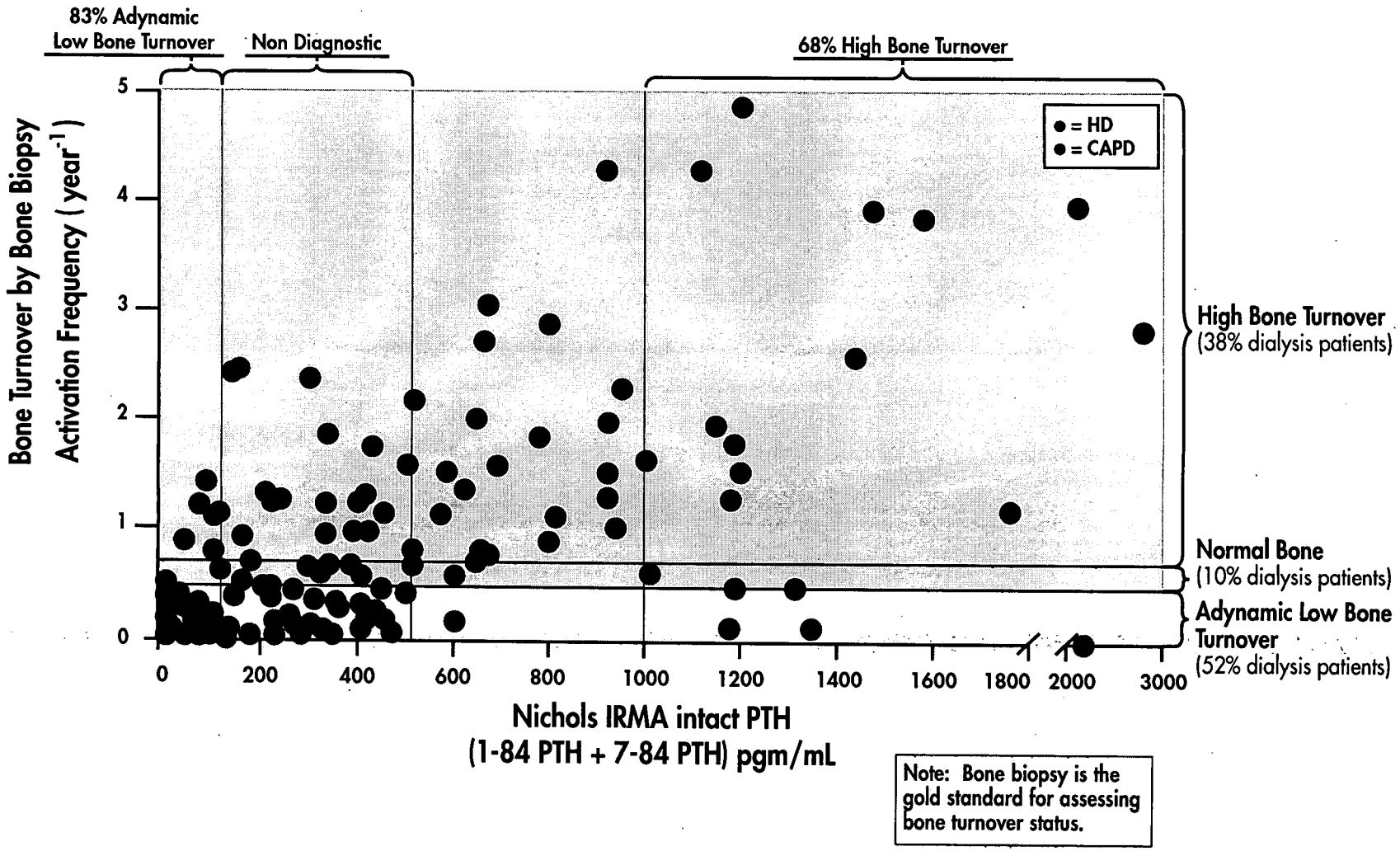


Price PA, Williamson MK, Minh Thi Nguyen T, Than TN. *J Biol Chem 2003; Oct 24.*

The Commonly Used Intact PTH Assay That Does Not Distinguish Between 1-84 PTH and 7-84 PTH

Misidentifies Adynamic Bone Disease Patients with PTH Values That are Too High Resulting in Overdosing of Vitamin D with Accelerated Arterial Calcification and Mortality

When Assessed by Bone Biopsy, the Intact PTH Assay was Found to be Non-Predictive of Bone Turnover (Except for <100 pgm/mL)



Faugere M-C, et al. Improved Assessment of Bone Turnover by the PTH 1-84/Large C-PTH Fragments Ratio in ESRD Patients. *Kidney Int 2001; 60:1460-1468.*

Qi Q, et al. Predictive value of serum parathyroid hormone levels for bone turnover in patients on chronic maintenance dialysis. *Am J Kidney Dis 1995; 26:622-31.*

Intact PTH is Non Diagnostic of Bone Turnover in African Americans

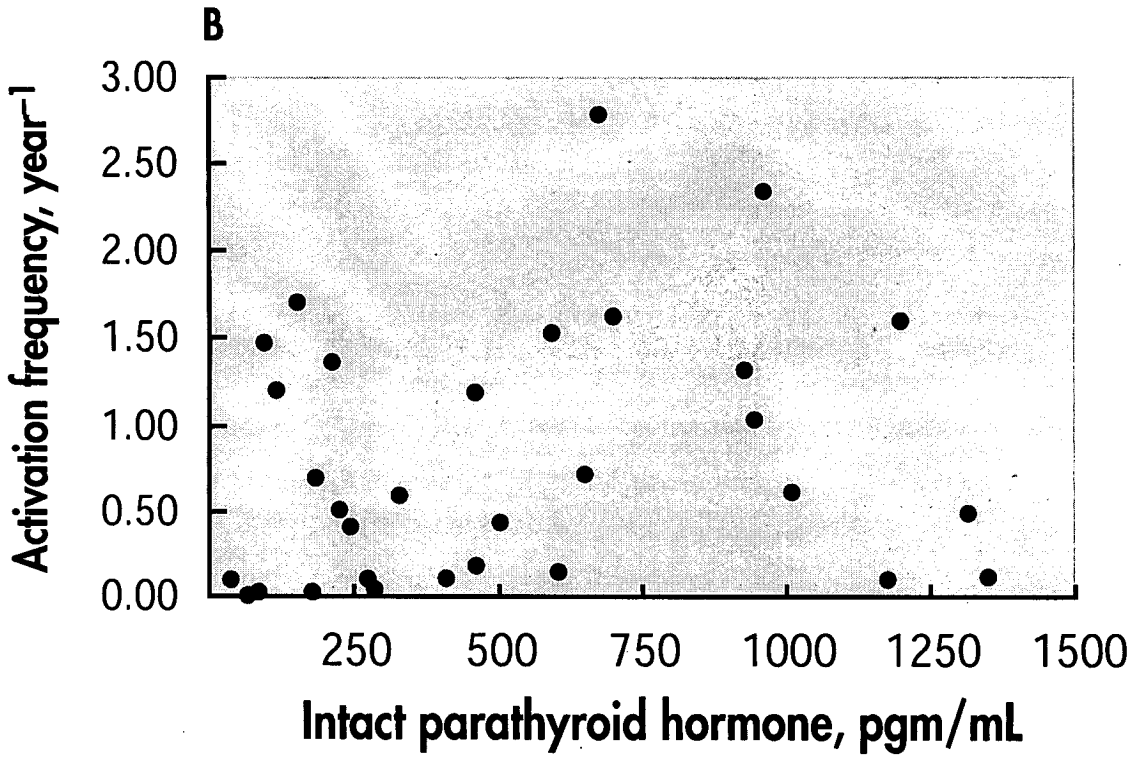


Fig. 1. Correlation between intact parathyroid hormone and activation frequency in *(A)* Caucasians (r = 0.60, *P* < *0.01*), and *(B)* African Americans (r = 0.22, *P* = *NS*).

African Americans make up 29% of dialysis population (USRDS) and 12% of population (US census)

Sawaya B P, Butros R, Naqvi S, et al. Difference in bone turnover and intact PTH levels between African American and Caucasian patients with end-stage renal disease. *Kidney Int 2003; 64:737–742.*

The Average Intact PTH for Adynamic Low Bone Turnover in African Americans is the Same as the Average Intact PTH for High Bone Turnover in Caucasians

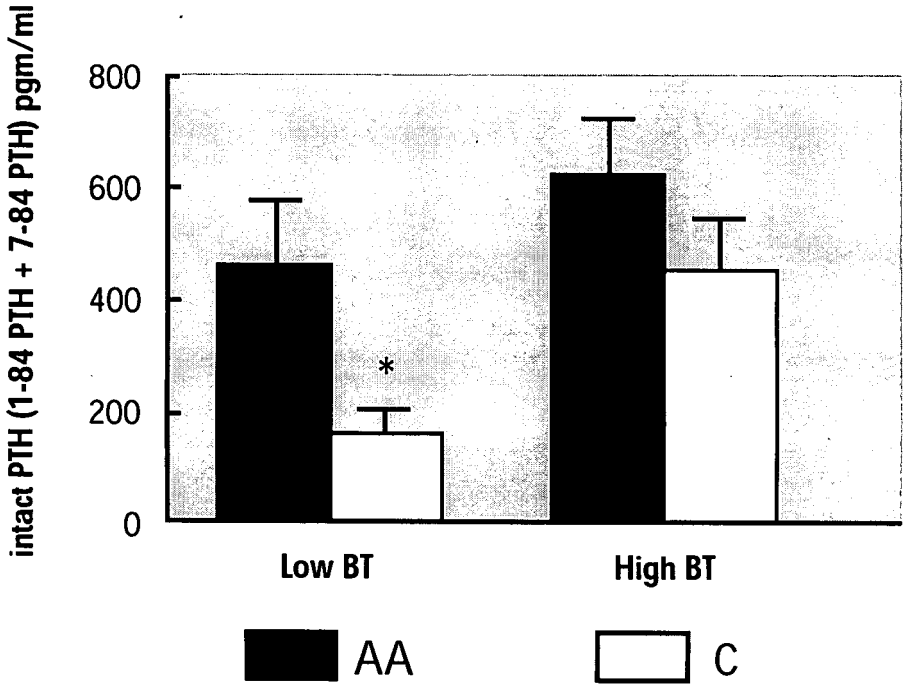
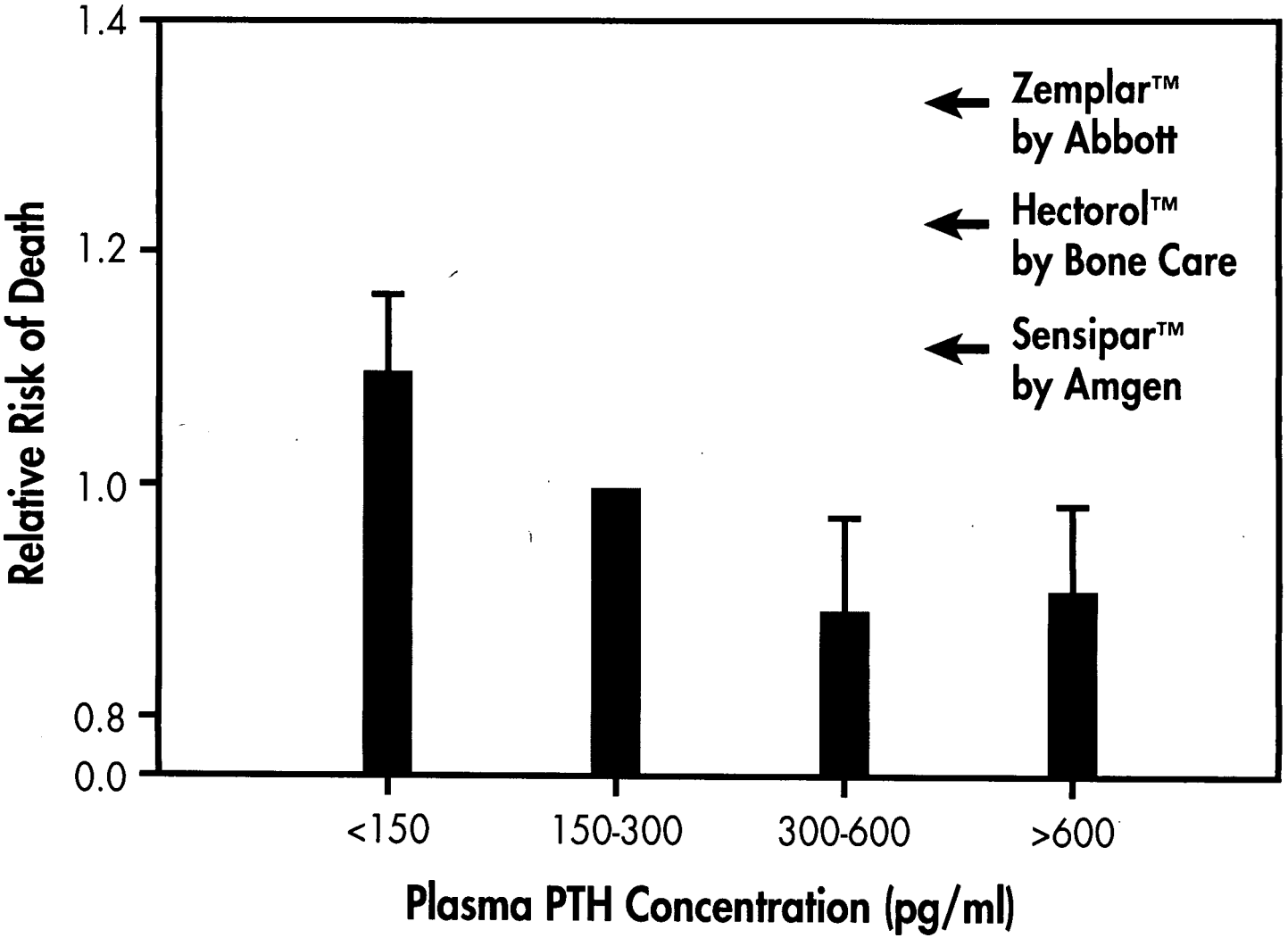


Fig. 2. Intact parathyroid hormone (PTH) in African Americans (AA) and Caucasians (C) with low and high bone turnover (BT). *P < 0.01 compared to PTH levels in all other groups.

African Americans make up 29% of dialysis population (USRDS) and 12% of population (US census)

Sawaya B P, Butros R, Naqvi S, et al. Difference in bone turnover and intact PTH levels between African American and Caucasian patients with end-stage renal disease. *Kidney Int 2003; 64:737–742.*

Mortality vs intact PTH in 40,538 Hemodialysis Patients

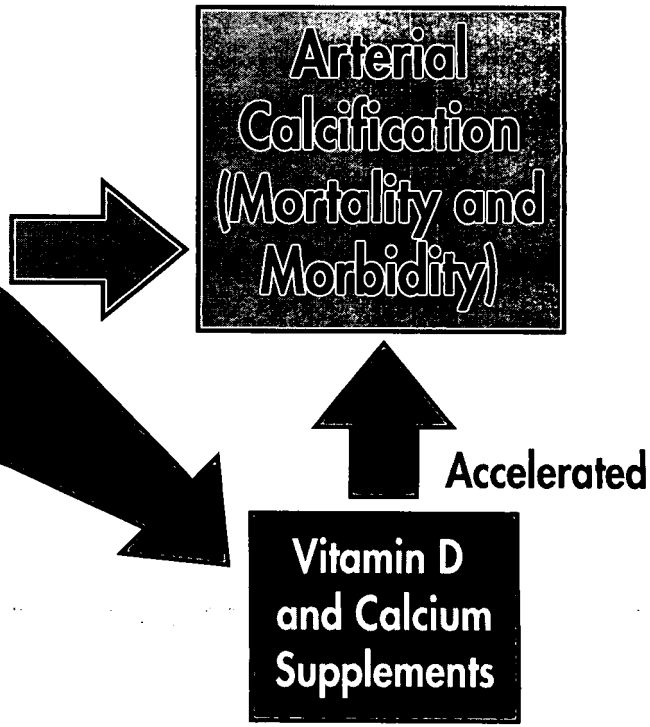


From the viewpoint of mortality using the intact PTH assay to adjust the dose of Zemplar™, Hectorol™, and Sensipar™ is not justified.

Block GA, Klassen PS, Lazarus JM et al. Mineral Metabolism, Mortality and Morbidity in Maintenance Hemodialysis. *J Am Soc Nephrol 2004; 15:2008-2218.*

Misdiagnosis and Consequences of Adynamic Bone Disease

Prevalence per Bone Biopsy	Bone Disease			Intact PTH (1-84 PTH + 7-84 PTH)	
10%–25%	Adynamic Bone Disease			Low	
30%–50%	**Adynamic Bone Disease**			**High**	
20%–40%	High Bone Turnover			High	



Faugere M-C, et al. Improved Assessment of Bone Turnover by the PTH 1- 84/ Large C- PTH Fragments Ratio in ESRD Patients. *Kidney Int 2001; 60: 1460-1468.*

Qi Q, et al. Predictive value of serum parathyroid hormone levels for bone turnover in patients on chronic maintenance dialysis. *Am J Kidney Dis 1995; 26: 622-31.*

London GM, Marty C, Marchais SJ, Guerin AP, Metivier F, De Vernejoul M- C. Arterial Calcifications and Bone Histomorphometry in End-Stage Renal Disease. *J Am Soc Nephrol 2004; 15: 1943-1951.*

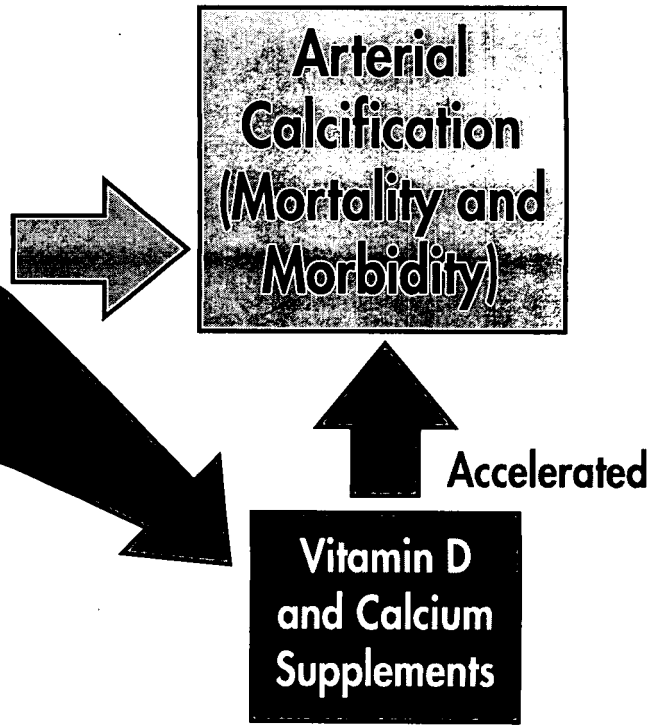
Blacher J, Hypertension 2001; 38: 938-942

Using a Specific 1-84 PTH Assay that Does Not Measure 7-84 PTH

Accurately Identifies Patients with Adynamic Bone Disease & Saves Them From Vitamin D Overdosing and the Mortal Arterial Calcification that Follows

Misdiagnosis and Consequences of Adynamic Bone Disease

Prevalence per Bone Biopsy	Bone Disease	1-84 PTH	7-84 PTH	Intact PTH (1-84 PTH + 7-84 PTH)	
10%–25%	Adynamic Bone Disease	Low	Low	Low	
30%–50%	**Adynamic Bone Disease**	**Low**	**High**	**High**	
20%–40%	High Bone Turnover	High	Low	High	



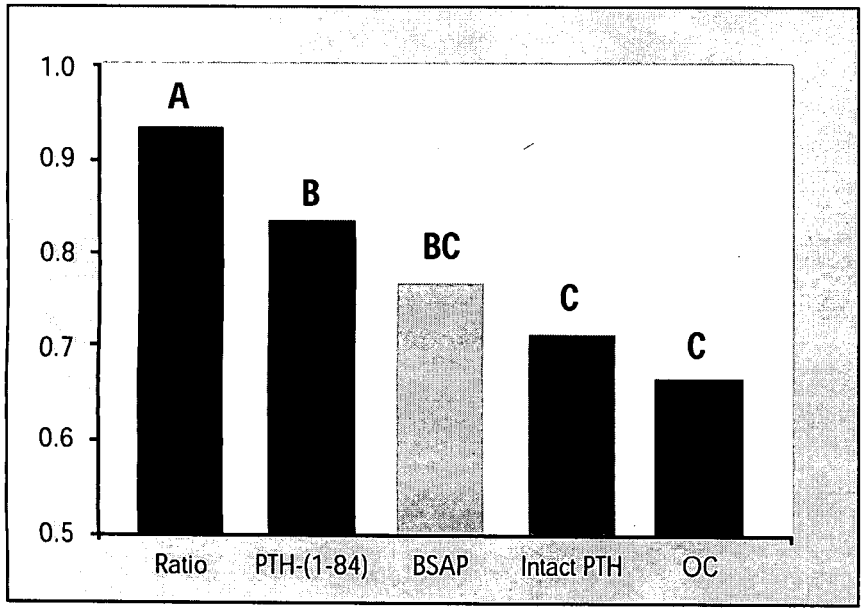
Faugere M-C, et al. Improved Assessment of Bone Turnover by the PTH 1- 84/ Large C- PTH Fragments Ratio in ESRD Patients. *Kidney Int 2001; 60: 1460-1468.*

Qi Q, et al. Predictive value of serum parathyroid hormone levels for bone turnover in patients on chronic maintenance dialysis. *Am J Kidney Dis 1995; 26: 622-31.*

London GM, Marty C, Marchais SJ, Guerin AP, Metivier F, De Vernejoul M- C. Arterial Calcifications and Bone Histomorphometry in End-Stage Renal Disease. *J Am Soc Nephrol 2004; 15: 1943-1951.*

Blacher J, Hypertension 2001; 38: 938-942

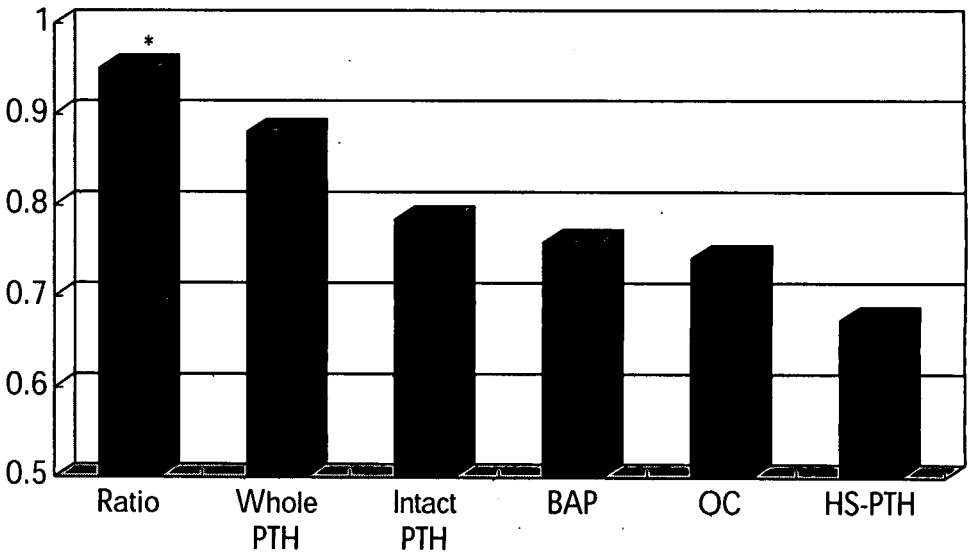
Dr. Malluche's Bone Biopsy Study Ranking Bone Markers for Accurate Prediction of Bone Turnover



Area under the curve (AUC) of the receiver-operator characteristics (ROC) curves for PTH-(1-84)/C-PTH fragments ratio, PTH-(1-84), bone-specific alkaline phosphatase (BSAP), intact PTH, and osteocalcin (OC). Values with the same letter are not significantly different.

Faugere M-C, Geng Z, Mawad H, et al. Improved Assessment of Bone Turnover by the PTH 1-84/Large C-PTH Fragments Ratio in ESRD Patients. *Kidney Int 2001; 60:1460-1468.*

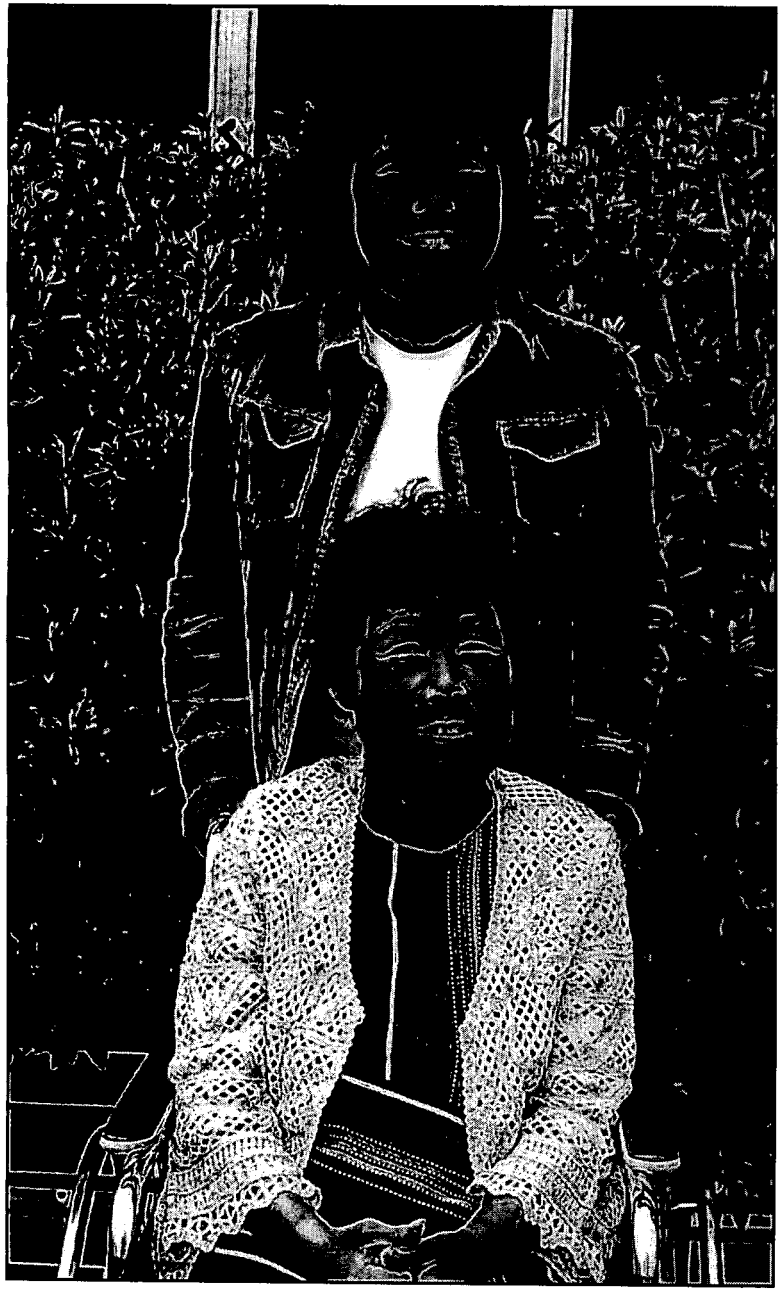
Dr. Tokumoto's Bone Biopsy Study Ranking Bone Markers for Accurate Prediction of Bone Turnover

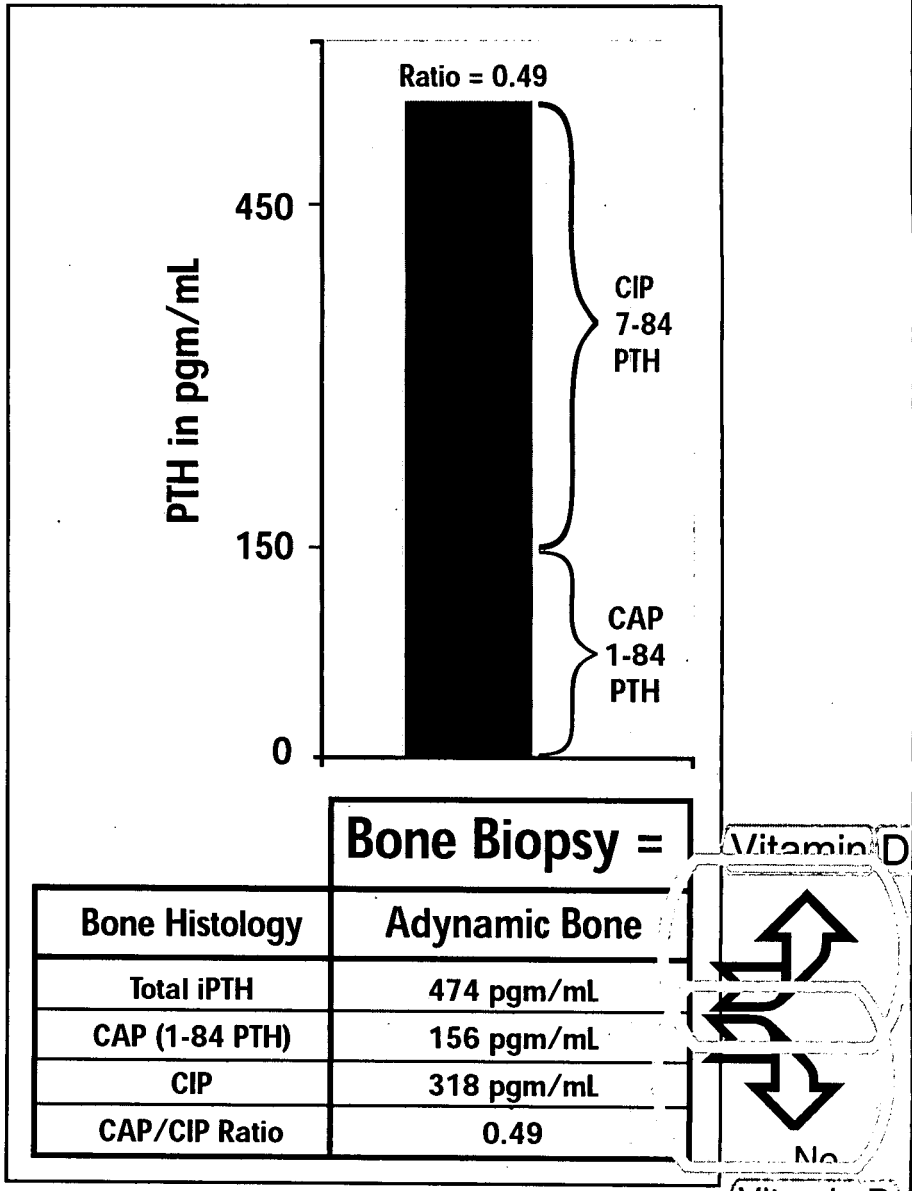


*p<0.05 vs. HS-PTH (Hanley-MacNeil test)

Tokumoto A. Superior Assessment of Bone Turnover in ESRD Patients by the 1- 84 PTH/ Large C Terminal PTH Fragments Ratio – A Bone Biopsy Study. *J Am Soc Nephrol 2003(Nov); 14:702.*

The Specific and Accurate PTH Assay that Does Not Measure 7-84 PTH Saved Michiko from Vitamin D Over Dosing & Further Calcification

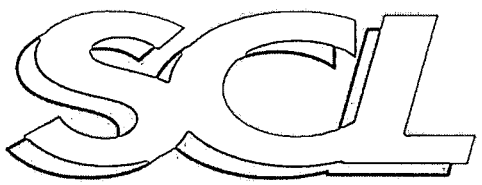




Bone Biopsy =	Vitamin D
Bone Histology	Adynamic Bone
Total iPTH	474 pgm/mL
CAP (1-84 PTH)	156 pgm/mL
CIP	318 pgm/mL
CAP/CIP Ratio	0.49

No Vitamin D

Tokumoto A. Case Study of Patient with Adynamic Low Bone Turnover Disease that Eluded Diagnosis – Comparison of PTH Ratio with Other Markers of Bone Turnover. *J Am Soc Nephrol 2003(Nov); 14:596.*



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